MIRECC

MENTAL ILLNESS RESEARCH, EDUCATION AND CLINICAL CENTER

Improving the long-term outcome of patients with serious mental disorders

MINDVIEW

Fall 2002

Genetics of Schizophrenia

by Louise Mahoney

Why Study Genetics?

It is clear that there is a strong genetic component to schizophrenia and other psychotic disorders, but many details of how genes contribute to these diseases are still unknown. By studying the transmission of schizophrenia from parent to offspring and the underlying biological mechanisms of this disease, researchers may be able to improve diagnosis and treatment. Developing a better understanding of how genes contribute to the development of psychotic disorders may help to reduce the self-blame that clients and families often feel and also may help to reduce the stigma that affected individuals experience.

What is the evidence for a genetic basis of schizophrenia?

Schizophrenia occurs in about 1% of the general population. Studies have shown that the occurrence of schizophrenia in families with a history of psychotic disorders is higher, as high as 13%, providing support for a genetic component of this disease. Additional support for the "heritability" of schizophrenia comes from studies of twins. If schizophrenia is inherited, then we would expect that the identical twin of an individual with schizophrenia (sharing 100% of their genes) would have a higher rate of schizophrenia than a fraternal twin (sharing 50% of their genes). Indeed, researchers have found that identical twins are more likely to have schizophrenia than fraternal twins.

Adoption studies have also helped researchers understand the heritability of schizophrenia. Investigators studied both biological and adoptive families of individuals with schizophrenia. If genes are more important than environment, then the rate of schizophrenia in biological relatives of individuals with schizophrenia should be high. If environmental and cultural factors are more important, the occurrence of schizophrenia should be higher in adoptive rather than biological relatives. The results of these studies indicate that inherited biological factors play a large role in schizophrenia.

How is Schizophrenia inherited?

Presently, it is unclear exactly how schizophrenia is inherited. However, schizophrenia is thought to be a complex genetic disorder because its inheritance pattern is not consistent with strict Mendelian inheritance (one gene is responsible for a particular trait or disorder). Examples of diseases that are caused by alterations in a single gene are cystic fibrosis, which can be inherited when both parents carry the gene (an autosomal recessive disorder), Huntington's disease, which can be inherited from one parent carrying the defective gene (an autosomal dominant disorder), and hemophilia which is generally passed from mother to son on the X chromosome (a sex-linked recessive disorder). The frequency of inheritance of these three genetic disorders can be predicted based on well-established statistical models.

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Neuroprotection: New Treatment Possibilities

by Andrius Baskys, MD, PhD

Injury and death of brain cells (neurons) underlie many brain disorders and often result in motor, cognitive, behavioral, and emotional disturbances. By understanding the mechanisms that govern brain cell death, scientists may be able to develop new treatments to prevent the problems associated with brain disorders, such as stroke, Alzheimer's disease, and even schizophrenia.

Protect Neurons: Prevent Excitotoxicity

Neuroprotection refers to the prevention of nerve cell death in the adult brain. Nerve cell death can occur in response to a variety of insults, such as ischemia (sudden interruption of blood flow to the brain that occurs in a stroke). Nerve cell death following ischemia occurs through a process referred to as *excitotoxicity*, which is the overactivation of normal chemical processes that regulate the function of the neuron. Under normal circumstances, glutamate, an important chemical substance involved in the communication between nerve cells, is released and interacts with different types of receptors located on other neurons. It is involved in the opening of small channels so sodium and calcium can enter the neuron. During excitotoxicity, excessive amounts of glutamate are released resulting in large quantities of sodium and calcium entering the neuron and initiating the chemical reactions that ultimately kill the cell.

Scientists have found that some glutamate receptor subtypes, those that operate sodium and calcium channels, are involved in nerve cell death. One type, the NMDA receptor, is particularly lethal to the nerve cell when activated. Although blocking NMDA receptors with new medications is very effective in reducing ischemic cell death in experimental models, clinical usefulness of this approach has been limited because of severe side effects

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LETTER FROM THE DIRECTOR

Stephen R. Marder

Genetics of Schizophrenia

This issue of Mindview focuses on genetics, an important vehicle for understanding complex illnesses such as schizophrenia. As a research tool, modern genetics has already led to important discoveries in a number of areas of medicine. Progress has been less dramatic in psychiatric illnesses, but the potential for major advances is extremely exciting.

Although it is clear that genetic factors play a major role in determining who will and who will not develop schizophrenia, nongenetic factors are also important. For example, monozygotic or identical twins have identical genes. This explains why if one monozygotic twin develops schizophrenia, there is a high likelihood that the other will develop the illness. However, the chances are well below 100%. This indicates that factors in the individual's environment can interact with genes to determine the vulnerability to the illness. These factors may include factors such as the blood flow during fetal development or stresses that may affect one of the twins.

The results from genetic studies also indicate the complexity of schizophrenia. A large number of studies have attempted to locate a single gene that is associated with schizophrenia. This search has been unsuccessful. Schizophrenia appears to be an illness that results from the effects of a number of genes in widespread locations. The illness may result from the additive effects of multiple genes when they are combined with the effects of certain environmental factors. For obvious reasons, illnesses with this level of complexity are much more difficult to characterize. This probably explains why reports of genes that are related to schizophrenia often create excitement which is later diminished when scientists fail to replicate these findings.

The MIRECC is carrying out a number of studies that may improve our understanding of the genetics of schizophrenia. Drs. John Kelsoe and Niculescu are using animal models to study genes that may affect the vulnerability to developing psychosis. Dr. David Braff is studying characteristics of an individual that may be associated with an illness, but are not the illness itself. For example, the manner in which a person processes certain information may be inherited and may be a factor associated with schizophrenia. On the other hand, all individuals with this abnormality may not develop schizophrenia. Both research groups are using methods of genetics research to improve our understanding of the biology of schizophrenia. ◆

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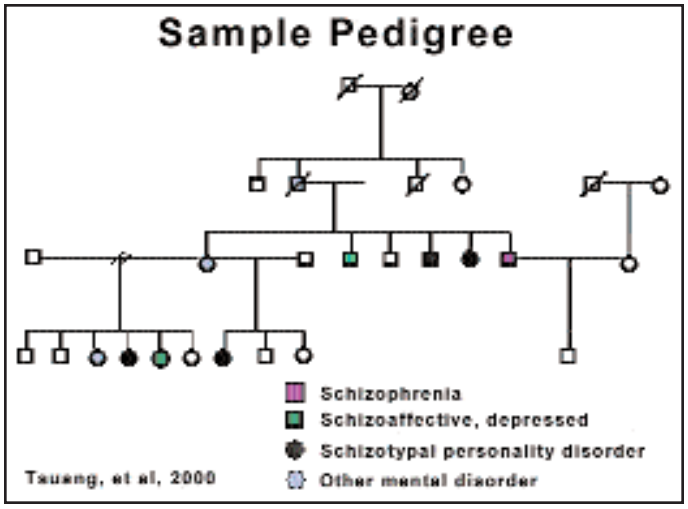
In contrast, studies of inheritance patterns within families (pedigree studies) have found that occurrence of schizophrenia is not as high as it should be if it were caused by a mutation in a single gene. Rather, schizophrenia has many features in common with other complex genetic traits such as heterogeneity (evidence that mutations in different genes can produce the same result), polygenic inheritance (the additive effects of several genes contribute to the disease), and incomplete penetrance (the fact that not everyone who carries the disease gene becomes ill). When a disease involves complex genetic factors it is difficult to formulate a simple statistical model of inheritance. One model that has received support is the multifactorial polygenic (MFP) model, which proposes that the underlying processes involved in schizophrenia are influenced by many genes. These genes are located on many chromosomes and have variable and additive effects on the susceptibility to schizophrenia. In this model, many genetic mutations combined with environmental influences are needed before schizophrenia will develop.



To determine how a disorder, such as schizophrenia, is inherited, researchers must first isolate the genes responsible for the disease. This is accomplished by linkage studies, which make use of well-characterized alternate versions of genes (alleles) in non-coding regions of the DNA and well-defined statistical models. These alternate versions of

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The Genetic Code

The blueprint for each human being is contained in the set of 23 chromosome pairs found in the nucleus of every cell. This group of 46 chromosomes is known as the human genome and contains a complete set of genetic instructions. Each chromosome is made from two deoxyribonucleic acid (**DNA**) strands and protein, forming a tightly coiled, complex three-dimensional structure. Each strand of DNA is a linear sequence of distinct subunits containing one of four organic bases which pair with complementary subunits on the opposite DNA strand. These form the ***base pair*** coding unit of the human genome. A sequence of three base pairs, a ***codon,*** defines each amino acid, the building blocks of protein. There is more than one codon for each amino acid. The ***genetic code*** is the set of all possible codons used by the cell to manufacture protein.

Protein synthesis is a process whereby the codons are "read" (this is called ***transcription***) forming another long molecule, messenger RNA (***mRNA***). The mRNA is again "read" (this is called ***translation***) 3 base pairs at a time but this time the process forms long amino acid chains which become the protein molecules in the cell. Alterations in base pair sequences often occur. Some alterations result in alternate versions of a gene, called ***alleles***, with normal function. Other alterations in the codons can result in non-functional proteins and can lead to disease. These are called ***mutations***.

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genetic material have been mapped throughout the human genome and are referred to as genetic markers. If a marker is located close to the gene responsible for a disease, then the affected family member should have that marker on his/her DNA and the non-affected family members would not. Analysis of DNA in affected families participating in linkage studies have uncovered genes with possible involvement in schizophrenia on chromosomes 1q, 5q, 6p, 10p, 11q, 13q, 15q, 18p and 22q (q and p refer to the long and short arms of the chromosomes respectively). More research is needed to confirm these results and to understand how these genes contribute to the development of schizophrenia.

New Developments: Genomics

New areas of study and new techniques that may improve the understanding of the genetics of schizophrenia are being developed. A relatively new field of genetics is genomics, the study of genes and their function. New techniques, such as microarray technology, allow scientists to study selected genes. Microarrays utilize the new "gene chip" technology where an enormous amount of DNA is attached to a small slide or chip and then allowed to bind to fluorescently labeled mRNA from the cells being studied.

Some MIRECC investigators are using microarrays to the study mania and psychosis. Using an animal model to mimic to psychosis associated with mania, they were able to localize regions of the rat genome responsible for these manic and psychotic characteristics. When they combined the information from the rat genes with data from published human linkage studies, they found several genes that overlapped. One common gene, G protein-coupled receptor kinase 3 (GRK3), is used for communication between nerve cells by a variety of neurotransmitters. This gene has been isolated to a region of chromosome 22 and has been implicated in other studies of both psychosis and bipolar disorder. This method of combining of information from both animal and human genomes has been termed "convergent functional genomics" and is becoming an important technique for studying the transmission of schizophrenia.

One other technique for studying the genetics of schizophrenia, the identification of endophenotypes, is being used by a different group of MIRECC investigators. An endophenotype is an attribute associated with a genetic disorder that is not necessarily visible to the human eye but is reliably measured in the laboratory (for example, abnormalities in brain waves). Many of these characteristics are subtle physiological processes, and researchers have found that individuals with schizophrenia, as well as their unaffected family members, have abnormalities in some of these processes. For example, both affected and nonaffected family members have impairments in the processing of some sensory input (sensory gating) and alterations in eye movements. Understanding the inheritance of endophenotypes and their underlying genetic mutations may provide important information regarding the transmission of schizophrenia.

Conclusion

Remarkable progress has been made in our quest to determine the transmission of schizophrenia and its underlying biological mechanisms. Studying the inheritance patterns of psychotic disorders has led to the localization of genes that may be responsible for psychotic symptoms; the development of "functional convergent genomics" has helped identify what biological mechanisms may be impaired in psychosis; and the study of endophenotypes may provide researchers with a useful tool to better understand the inheritance of schizophrenia. Scientific advances, such as these, will guide the development of better treatments for schizophrenia and other psychotic disorders.◆

Neuroprotection *(Continued from page 1)*

such as severe hallucinations and other psychiatric symptoms. A more promising approach to prevent nerve cell death may be to prevent the cascade of chemical reactions that occur after the NMDA receptor is activated. There is evidence for possible neuroprotective properties of apigenin, which is found naturally in chamomile, coriander, onion and citrus fruit.

Pre-Conditioning

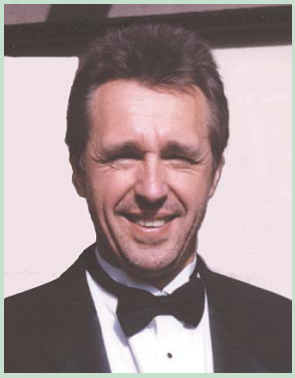
There are other ways that neuroprotection may occur. While large amounts of glutamate cause nerve cell death, moderate amounts may protect neurons from damage caused by their subsequent exposure to glutamate at high concentrations. This phenomenon is sometimes referred to as "preconditioning" and has been observed in humans. A recent study found that patients who had brief episodes of cerebral ischemia (transient ischemic attacks; TIAs) prior to experiencing a stroke, had better clinical outcomes than those individuals who did not have TIAs. Researchers believe that activation of another type of glutamate receptor, one that initiates a complex chemical reaction which alters the metabolism inside the cell, may be crucial for the preconditioning to occur. Results of some studies suggest that the sensitivity of the neuron to excitotoxicity is regulated by a subtype of the glutamate receptor. That is, if a moderate amount of glutamate is present to act on these metabotropic receptors, then the neuron is not as susceptible to death when very high doses of glutamate interact with the more lethal (excitotoxic) NMDA receptor. Developing drugs that work at the metabotropic glutamate receptors to help protect neurons from excitotoxicity may present novel opportunities for the prevention of pathological processes associated with cerebral ischemia and stroke.

Neuroprotection and schizophrenia

Abnormal cell death does occur in schizophrenia, but it is not yet known whether excitotoxicity plays a role. Researchers, however, suspect that glutamate and the NMDA receptor are involved in the production of psychotic symptoms. For example, when people ingest drugs, such as PCP, that block glutamate activity, they often experience hallucinations. This observation suggests new directions for studying the biological mechanisms that cause schizophrenia; and consequently, new opportunities to develop drugs that treat schizophrenia. ◆

THE FACES OF MIRECC

Andrius Baskys, M.D., Ph.D.



Andrius Baskys, M.D., Ph.D.

Dr Baskys is a geriatric psychiatrist at the VA Medical Center in Long Beach and Assistant Professor of Psychiatry and Human Behavior at U.C., Irvine. He did his psychiatry residency at the University of Toronto and continued his training at the McMaster University as a fellow in geriatric Psychiatry. Dr Baskys has studied neuroplasticity in such prestigious institutions as University College, London, Brain Institute, Moscow, University of Toronto and UCSF. He is a recipient of the Alzheimer's research scholarship award and Medical Council of Canada award.

Dr Baskys authored or co-authored three books on psychopharmacology and over 90 publications, presentations and reports. He is a Director of the Memory disorders program at the Long Beach VA and a co-director of the inpatient Psychogeriatric unit and runs the Molecular physiology laboratory. His research interests include pathophysiology and treatment of psychosis in patients with neurodegenerative disorders and Lewy body dementia. His laboratory is engaged in studies of molecular mechanisms of neuroprotection.

You have an MD and a PhD. Why did you choose to get both?

I became interested in research while in medical school. My first research assignment was investigating visual information processing in cats. It soon became evident that without understanding the mechanisms of memory, it is not possible to understand how the cat sees the world. I began to study memory, specifically, synaptic plasticity and long-term potentiation in the hippocampus, the key brain structure involved in short-term memory storage. This led to studies of the neurotransmitters, serotonin and glutamate, which are used in the hippocampus. Now, I am focused on studying the mechanisms of action of these neurotransmitters with the aim of developing and evaluating drugs that would treat such diseases as Alzheimer's, psychosis, and schizophrenia.

In what ways does this combination of clinical training in psychiatry and research training in neuroscience influence your work?

Psychiatry is a science that has many interesting questions to tackle for a probing mind. One of them is the question of how nerve cell death and survival contribute to psychiatric symptoms, such as memory loss and hallucinations, commonly encountered in patients suffering from Alzheimer's or Lewy body disease. There is no treatment for these conditions, but some of the drugs psychiatrists use can make symptoms better. We take these drugs to the laboratory and study how they affect nerve cell function and survival. We use animal models of these diseases to conduct experiments that should provide us with a better understanding of how these psychiatric drugs work. The more we know about how drugs work, the more likely we are to develop new drugs that improve nerve cell survival and consequently, further reduce the troubling symptoms that people experience.

How do you think the study of cellular/molecular neurobiology and genomics will affect the our understanding of psychiatric disorders and their treatment?

In theory, advances in molecular biology techniques and genomics could help researchers cure most diseases, including mental illnesses. In reality, we are far from this goal. One huge obstacle in understanding the causes and cures of many diseases is the process by which efficacious drugs get from the laboratory to the clinics. The path between discovery in the laboratory and clinical use of a drug is long, extremely costly and not always straightforward. Finding ways to streamline this process should be a priority, and many researchers are involved in developing ways to improve the translation of impor-

Mental Illness Research, Education and Clinical Center

VA Desert Pacific Healthcare Network
Long Beach VA Healthcare System
Mental Healthcare Group 06/116A
5901 E. 7th Street
Long Beach, CA 90822

Director
Stephen R. Marder, M.D.

Co-Directors, Education and Dissemination Unit
Sonia Ancoli-Israel, Ph.D.
Christopher Reist, M.D.

MindView Editors
Danielle Kukene
Laurie Lindamer, Ph.D.
Louise Mahoney, M.S.

Email: info@mirecc.org
Phone: (562) 826-8000 x2546
Fax: (562) 826-8165

MIRECC

MIRECC
Long Beach VA Healthcare System
Mental Healthcare Group 06/116A
5901 E. 7th Street
Long Beach, CA 90822